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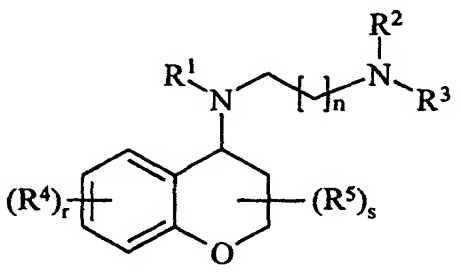
(54) Title: CHROMAN DERIVATIVES AGAINST NEUROLOGICAL DISORDERS



(I)

(57) Abstract: Methods for the use of compounds of formula (I) for treatment of neurological disorders, wherein n, r and s are as defined in the specification and R^1, R^2, R^3, R^4 and R^5 are various substituents, also as defined in the specification, such compounds and pharmaceutical compositions containing such compounds.

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CHROMAN DERIVATIVES AGAINST NEUROLOGICAL DISORDERS

The present invention relates to chemical compounds, in particular chromans, to processes for their preparation and to chemical intermediates useful in such processes. The present invention further relates to chromans, to pharmaceutical compositions containing them and to their use in methods of therapeutic treatment of animals including man, in particular in the treatment of neurological disorders.

Neurological disorders, for which the present compounds are useful, include stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. The compounds useful in the present invention act by selectively binding to the [^{3}H]-emopamil binding site. Compounds with selective action at the [^{3}H]-emopamil binding site exhibit fewer associated side effects such as hypotension seen with emopamil or behavioural manifestations seen with ifenprodil.

Background

Emopamil has classically been thought of as a neuroprotective agent whose efficacy is most likely derived from actions at either voltage-sensitive calcium channels (VSCC) or 5-HT_2 receptors. An apparent paradox to this logic is that verapamil, although chemically and pharmacologically very similar to emopamil, is not neuroprotective. While the lack of neuroprotective efficacy by verapamil was initially explained by lack of CNS penetration, recent studies suggest other factors may be involved (Keith et al., Br. J. Pharmacol. 113: 379-384, 1994).

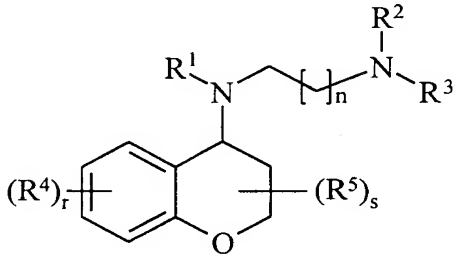
[^{3}H]-Emopamil binding defines a unique high affinity site that is not related to VSCC, is found in the brain, but is most prevalent in the liver (Moebius et al., Mol. Pharmacol. 43: 139-148, 1993). Moebius et al. have termed this the "anti-ischaemic" binding site on the basis of high affinity displacement by several chemically disparate neuroprotective agents. In liver, the [^{3}H]-emopamil binding site is localised to the endoplasmic reticulum.

Neuroprotective compounds are known, for example emopamil and ifenprodil, that exhibit high affinity for the [^{3}H]-emopamil binding site. However these are not selective inhibitors and exhibit activity either at neuronal VSCC, the polyamine site of the NMDA receptor (N-Methyl-D-aspartate) and/or the sigma-1 binding site.

Summary of the Invention

In one aspect of the present invention a new method for using compounds having selective action at the [^{3}H]-emopamil binding site and that are neuroprotective without acting directly at either VSCC or NMDA receptors is disclosed.

Compounds of the invention that have selective action at the [^{3}H]-emopamil binding site are compounds of formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl;

R^4 at each occurrence is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R^4 may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the value of R^5 may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In another aspect of the present invention, new pharmaceutical compositions containing compounds of formula (I), or *in vivo*-hydrolysable esters, amides or carbamates thereof, together with a pharmaceutically-acceptable carrier such as an excipient, diluent or stabilizer or combinations thereof as further defined herein are disclosed.

In a further aspect of the present invention, the use of a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [^{3}H]-emopamil binding site in a warm-blooded animal is disclosed.

In yet a further aspect of the present invention, novel compounds are disclosed which are compounds of formula (I) with a proviso wherein in such compounds:

if r is 1, R^4 is a 6-linked cyano moiety, s is 2 and both R^5 moieties are 2-linked methyl, n is 1, and R^1 and R^2 are both H, then R^3 is not phenyl or benzyl;

if r and s are both 0, R^1 is H and n is 2, then R^1 and R^2 are not both ethyl or not both H, or if r and s are both 0, R^1 is H and n is 1, then R^1 and R^2 are not both ethyl.

Detailed Description of the Invention

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. A similar convention applies to "alkenyl", "alkynyl" and other radicals, for example "phenylC_{1-6}alkyl" includes 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

The term aryl refers to an unsaturated carbon ring. Preferably aryl is phenyl, naphthyl or biphenyl. More preferably aryl is phenyl.

The term "heteroaryl" or "heteroaryl ring" refers to, unless otherwise further specified, a monocyclic-, bicyclic- or tricyclic-, 5- to 14-membered ring that is unsaturated or partially unsaturated, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring nitrogen atom may be optionally oxidised to form the N-oxide. Examples of such heteroaryls include thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, pyridyl-*N*-oxide, oxopyridyl, oxoquinolyl, pyrimidinyl, pyrazinyl, oxopyrazinyl, pyridazinyl, indolinyl, benzofuranyl, benzimidazolyl, benzothiazolyl, quinolyl, isoquinolinyl, quinazolinyl, xanthenyl, quinoxalinyl, indazolyl, benzofuranyl and cinnolinolyl.

The term "heterocyclyl" or "heterocyclic ring" refers to, unless otherwise further specified, a mono- or bicyclic-, 5- to 14-membered ring, that is totally saturated, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Examples of such heterocyclyls include morpholinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl and quinuclidinyl.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

In the present invention, examples of C_{1-6}alkyl include C_{1-4}alkyl such as methyl, ethyl, isopropyl and *t*-butyl;

examples of phenylC_{1-6}alkyl include phenylC_{2-6}alkyl such as phenylC_{1-4}alkyl such as phenylC_{2-4}alkyl such as benzyl, phenylethyl and phenylpropyl;

examples of C_{1-6}alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl;

examples of C_{1-6}alkoxy include methoxy, ethoxy and propoxy;

examples of C_{1-6}alkanoylamino include formamido, acetamido and propionylamino;

examples of C_{1-6}alkyl$S(O)_a$ where a is 0, 1 or 2 include C_{1-6}alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl;

examples of C_{1-6}alkylsulphonyl include mesyl and ethylsulphonyl;

examples of C_{1-6}alkanoyl include propionyl and acetyl;

examples of *N*-C_{1-6}alkylamino include *N*-methylamino and *N*-ethylamino;

examples of *N*,*N*-$(C_{1-6}alkyl)_2$amino include *N*,*N*-dimethylamino, *N*,*N*-diethylamino and *N*-ethyl-*N*-methylamino;

examples of C_{3-12}cycloalkyl include cyclopropyl and cyclohexyl;

examples of C_{3-12}cycloalkyl fused to a benzene ring are 1,2,3,4-tetrahydronaphthyl and 2,3-dihydroindenyl;

examples of C_{2-6}alkenyl include vinyl, allyl and 1-propenyl;

examples of C_{2-6}alkynyl include ethynyl, 1-propynyl and 2-propynyl;

examples of haloC_{2-6}alkyl include 2-chloroethyl and 2-bromopropyl;

examples of *N*-$(C_{1-6}$alkyl)sulphamoyl include *N*-methylsulphamoyl and *N*-ethylsulphamoyl;

examples of *N*,*N*-$(C_{1-6}alkyl)_2$sulphamoyl include *N*,*N*-dimethylsulphamoyl and *N*-methyl-*N*-ethylsulphamoyl;

examples of *N*-$(C_{1-6}$alkyl)carbamoyl include *N*-methylcarbamoyl and *N*-ethylcarbamoyl;

examples of *N*,*N*-$(C_{1-6}alkyl)_2$carbamoyl include *N*,*N*-dimethylcarbamoyl and *N*-methyl-*N*-ethylcarbamoyl, and

examples of C_{1-6}alkanoyloxy include propionyloxy, acetyloxy and formyloxy.

Preferably R^1 is hydrogen or C_{1-6}alkyl

More preferably R^1 is hydrogen or C_{1-4}alkyl.

Particularly R^1 is hydrogen or methyl.

More particularly R^1 is methyl.

In one aspect of the invention, preferably R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; wherein said C_{1-6}alkyl, is optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano,

amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl or C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl or heterocycle may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl.

In another aspect of the invention preferably R^2 and R^3 and the nitrogen atom to which they are attached in combination form a ring selected from 1,2,3,4-tetrahydroisoquinolinyl, morpholinyl, piperidinyl, pyrrolidinyl, homopiperidinyl and wherein said ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl.

In a further aspect of the invention, preferably R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl; or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic ring.

More preferably R^2 and R^3 are independently selected from methyl, ethyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl, piperidin-1-yl or morpholino ring.

Particularly R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl or piperidin-1-yl ring.

Preferably r is 0.

Preferably s is 0.

In one aspect of the invention preferably n is 1.

In another aspect of the invention preferably n is 2.

Therefore in a preferred aspect of the invention there is provided an compound of formula (I) as depicted above wherein:

R^1 is hydrogen or C_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic ring;

r is 0;

s is 0;

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a more preferred aspect of the invention there is provided a compound of the formula (I) as depicted above wherein:

R^1 is hydrogen or methyl;

R^2 and R^3 are independently selected from methyl, ethyl or benzyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl, piperidin-1-yl or morpholino ring;

r is 0;

s is 0;

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a particular aspect of the invention there is provided a compound of formula (I) as depicted above wherein:

R^1 is hydrogen or methyl;

R^2 and R^3 are independently selected from methyl or benzyl,

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl or piperidin-1-yl ring;

r is 0;

s is 0;

n is 1 or 2;

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

Preferred compounds of the invention are those of Examples.

A preferred aspect of the invention relates to any one of the Examples.

Preferred aspects of the invention relate to a compound according to formula (I) or a pharmaceutically-acceptable salt thereof.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N*,*N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is a sodium salt.

The compounds of formula (I) possess a chiral centre at the 4-position of the chroman ring. Certain compounds of formula (I) may also have other chiral centres, for example certain of the values of R^2, R^3, R^4, R^5 and certain of the optional substituents may possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diasteroisomers of compounds of formula (I) that inhibit the [^{3}H]-emopamil binding site.

The invention further relates to all tautomeric forms of the compounds of formula (I).

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms and that the invention encompasses all such solvated and unsolvated forms.

In vivo-hydrolysable esters, amides and carbamates are compounds that hydrolyse in the human body to produce the parent compound. Such esters, amides and carbamates can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo*-hydrolysable amides and carbamates include N-carbomethoxy and N-acetyl.

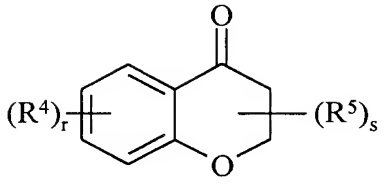
An *in vivo*-hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo*-hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo*-hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

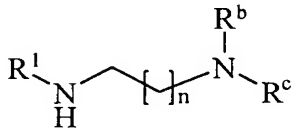
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof which process (wherein R^1, R^2, R^3, R^4, R^5, n, r and s are, unless otherwise specified, as defined in formula (I)) comprises of:

a) reacting a ketone of formula (II):



(II)

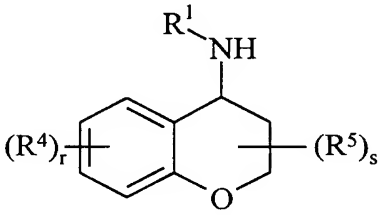
with an amine of formula (III):



(III);

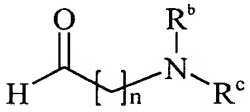
wherein R^b and R^c are R^2 and R^3 respectively, unless the value of R^2 and/or R^3 is hydrogen, in which case the appropriate R^b and/or R^c is a suitable amino protecting group such as those defined below; or

b) reacting an amine of formula (IV):



(IV)

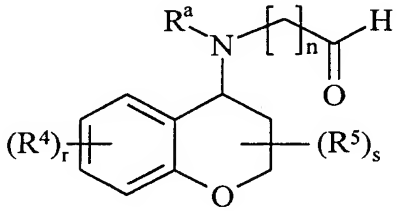
with an aldehyde of formula (V):



(V)

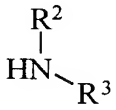
wherein R^b and R^c are as defined above; or

c) reacting an aldehyde of formula (VI):



(VI)

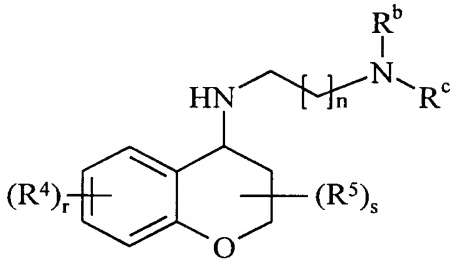
with an amine of formula:



(VII)

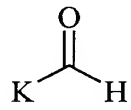
wherein R^a is R^1 unless the value of R^1 is hydrogen, in which case R^a is a suitable amino protecting group such as those defined below; or

d) if R^1 is C_{1-6}alkyl, reacting a compound of formula (VIII):



(VIII)

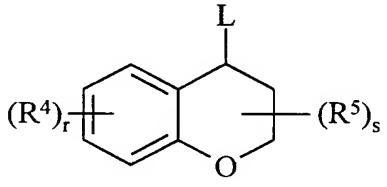
wherein R^b and R^c are as defined above, with a compound of formula (IX);



(IX)

wherein K is hydrogen or C_{1-5}alkyl; or

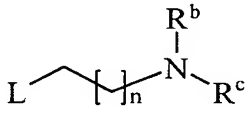
e) reacting a compound of formula (X):



(X)

wherein L is a suitable displaceable group, with an amine of formula (III); or

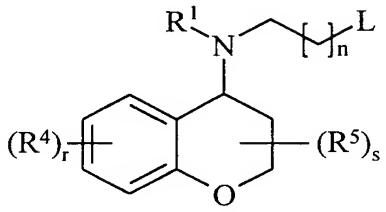
f) reacting an amine of formula (IV) with a compound of formula (XI):



(XI)

wherein L is a suitable displaceable group and R^b and R^c are as defined above; or

g) reacting a compound of formula (XII):



(XII)

wherein L is a suitable displaceable group, with an amine of formula (VII); or

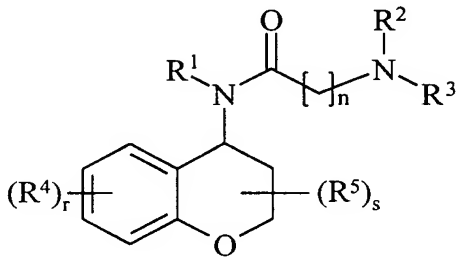
h) if R^1 is not hydrogen, reacting a compound of formula (VIII) with a compound of formula (XIII):

R^1-L

(XIII)

wherein L is a suitable displaceable group;

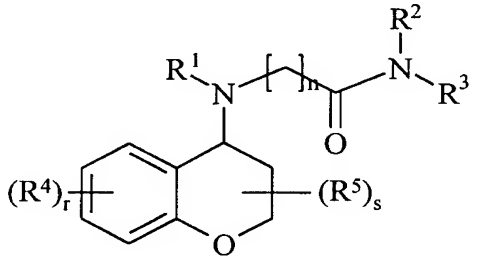
i) reducing a compound of formula (XIV):



(XIV)

or

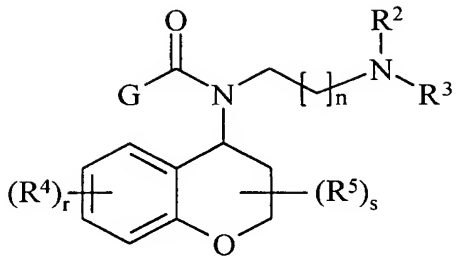
j) reducing a compound of formula (XV):



(XV)

or

k) if R^1 is not hydrogen, reducing a compound of formula (XVI):



(XVI)

wherein:

1) for preparing a compound wherein R^1 is methyl, G is a suitable displaceable group; or

2) for preparing a compound wherein R^1 is C_{2-6}alkyl, G is C_{1-5}alkyl;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups; or

iii) forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

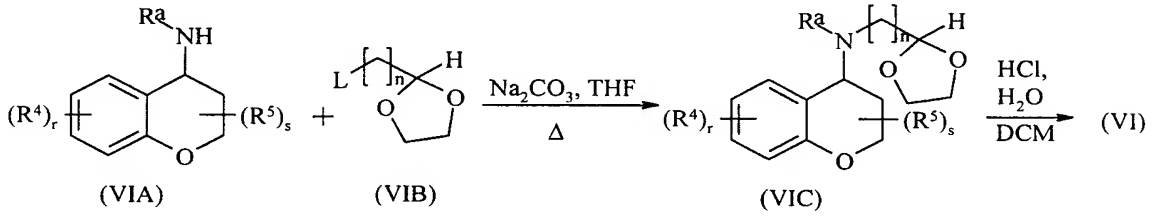
When G is a suitable displaceable group, suitable values for G are C_{1-6}alkoxy, for example methoxy or ethoxy.

Specific reaction conditions for the above reactions a), b), c) and d) are as follows:

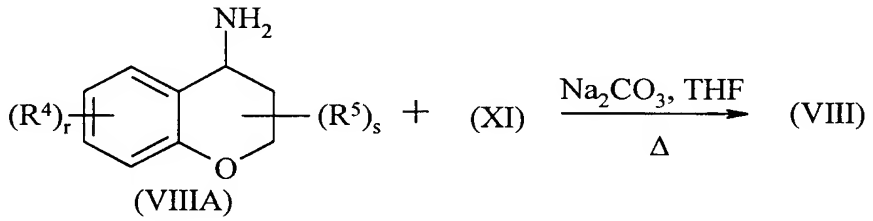
Ketones or aldehydes may be reacted with amines under standard reductive amination conditions. Imine formation may optionally be assisted with a Lewis acid for example titanium tetrachloride, in an inert solvent for example toluene. The reduction may occur for example in the presence of a reducing agent such as hydrogen and a hydrogenation catalyst (for example palladium on carbon), or zinc and hydrochloric acid, or sodium cyanoborohydride, or sodium triacetoxyborohydride, or sodium borohydride, iron pentacarbonyl and alcoholic potassium hydroxide, or borane and pyridine or formic acid. The reaction is preferable carried out in the presence of a suitable solvent such as an alcohol, for example methanol or ethanol, and at a temperature in the range of 0-50 °C, preferably at or near room temperature.

Compounds of formula (II), (III), (IV), (V), (VII) and (IX) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula (VI) may be prepared according to the following scheme:



Compounds of formula (VIII) may be prepared according to the following scheme:



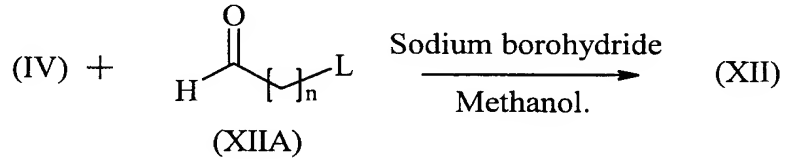
Compounds of formula (VIA), (VIB) and (VIIIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Specific reaction conditions for the above reactions e), f), g) and h) are as follows:

Amines and compounds with suitable leaving groups are reacted together under standard alkylation conditions. For example in the presence of a base, such as an inorganic base for example sodium carbonate or sodium hydroxide or in the presence of excess amine, in the presence of an inert solvent for example tetrahydrofuran, acetonitrile or toluene and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula (X), (XI) and (XIII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula (XII) may be prepared according to the following scheme.

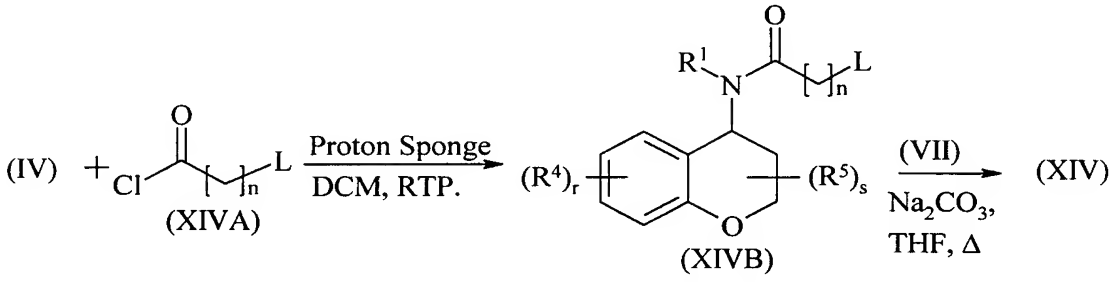


Compounds of formula (XIIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

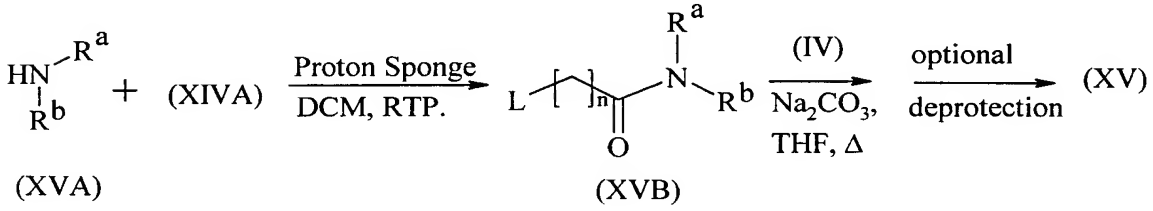
Specific reaction conditions for the above reactions i), j) and k) are as follows:

Compounds of formula (XIV), (XV) and (XVI) are reduced under standard reduction conditions for reducing an amide to an amine. For example, in the presence of a reducing agent such as borane, sodium borohydride or lithium aluminium hydride, in an inert solvent such as toluene or tetrahydrofuran, and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula (XIV) may be prepared according to the following scheme:

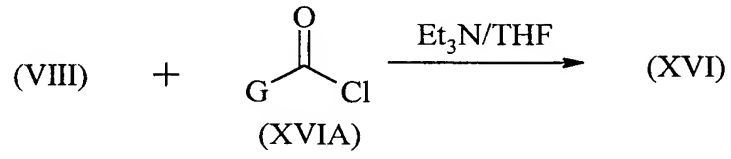


Compounds of formula (XV) may be prepared according to the following scheme:



wherein R^a, R^b and L are as hereinbefore defined.

Compounds of formula (XVI) may be prepared according to the following schemes:



Compounds of formula (XIVA) and (XVIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

When an optically active form of a compound of the formula (I) is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically

active starting material or by resolution of a racemic form of said compound using a conventional procedure.

An example of converting one compound of formula (I) into another compound of formula (I) is the conversion of R^1, R^2 or R^3 when they are hydrogen to a different R^1, R^2, or R^3. For example an alkyl group could be introduced by standard alkylation or reductive amination techniques, such as those described above.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an

arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I). To use compounds of formula (I) or a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate

thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical compositions of compounds of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions. A preferred route of administration is intravenously in sterile isotonic solution.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.05 to 75 mg/kg body weight (and preferably of 0.1 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention in association with a pharmaceutically-acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a compound of the formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula (I) and pharmaceutically-acceptable salts or an *in vivo*-hydrolysable ester, amide or carbamate thereof, for use as a medicament to inhibit the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method of inhibiting of the [^{3}H]-emopamil binding site in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore.

The following Biological Test Methods, Data and Examples serve to illustrate the present invention.

Biological Test Methods

^{3}H-Emopamil binding to guinea pig liver membranes

The method of (-)-^{3}H-emopamil binding was a modification of Zech, C., Staudinger R., Mühlbacher, J. and Glossmann, H. Novel sites for phenylalkylamines: characterisation of a sodium-sensitive drug receptor with (-)-^{3}H-emopamil. Eur. J. Pharm. **208**: 119-130, 1991. The reaction mixture contained:

Assay buffer: 10 mM Tris-HCl, 0.1 mM phenylmethylsulfonyl fluoride (PMSF), 0.2% bovine serum albumin (BSA), pH 7.4 at 4 °C.

Radioligand: 0.96 nM (-)-^{3}H-emopamil (Amersham).

Guinea pig liver membranes: 40mg/mL original wet weight.

Compounds: 1-300 nM.

Total volume: 500 µl.

This mixture was incubated for 60 minutes at 37 °C. The incubation was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenimine (PEI) and washed three times with 5 mL of wash buffer containing 10 mM Tris-HCl, 10 mM $MgCl_2$, 0.2% BSA, pH 7.4 at 25 °C. Specific binding was defined with 10 µM emopamil. In general compounds with an IC_{50} below 300nM in this test were of interest.

Guinea-pig liver membrane preparation:

Male guinea pigs were sacrificed by CO_2 asphyxiation with dry ice. The livers were

quickly excised and weighed and rinsed in membrane preparation buffer containing 10 mM Hepes, 1 mM Tris base-EDTA, 250 mM sucrose, pH 7.4. The livers were then minced, homogenised in 10 times volume with a motor driven Teflon-glass homogeniser with three strokes on ice. The homogenate was centrifuged at 1000 x g in a SS34 rotor for 5 minutes at 4 °C. The supernatant was filtered through 4 layers of gauze and then centrifuged at 8000 x g for 10 minutes at 4 °C. This resulting supernatant was centrifuged at 40,000 x g for 15 minutes at 4 °C. The resulting pellet was resuspended in assay buffer and centrifuged again at 40,000 x g for 15 minutes at 4 °C. This pellet was resuspended in assay buffer (2.5 fold with respect to original wet weight) and homogenised with one stroke with the Teflon-glass homogeniser. Aliquots of 1 mL were stored at -70 °C.

^{3}H-D-888 binding to rat brain cortical membranes

The method of ^{3}H-D-888 binding was a modification of Reynolds, I.J., Snowman, A.M. and Synder, S.H. (-)-[^{3}H] Desmethoxyverapamil labels multiple calcium channel modular receptors in brain and skeletal muscle membranes: differentiation by temperature and dihydropyridines. J. Pharmacol. Exp. Ther. **237**: no.3, 731-738, 1986.

The assay tubes contained the following:

assay buffer: 50 mM Hepes, 0.2% BSA, pH 7.4

radioligand: 1ηM ^{3}H-D888 (Amersham)

rat cortical membranes: 6 mg/mL original wet weight

compounds: 0.3-100 μM

Total volume: 1000 μl

This mixture was incubated for 60 minutes at 25 °C. The assay was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenamine (PEI) and washed three times with 5 mL of wash buffer containing 20 mM Hepes, 20 mM $MgCl_2$, pH 7.4. Specific binding was measured with 10 μM methoxyverapamil (D-600). This assay was used to determine in vitro selectivity of compounds vs. L-type voltage sensitive calcium channels, i.e. high affinity for the ^{3}H-D888 binding site would show a lack of selectivity.

Rat brain cortical membrane preparation

Male Sprague-Dawley Rats were sacrificed by decapitation and the brains were quickly excised. The cerebellum and brain stem were removed and discarded; and the rest of

the brain was rinsed in 320 mM sucrose. The brain was then homogenised in a 10-fold volume of 320 mM sucrose with a motor driven Teflon-glass homogeniser using 10 strokes on ice. The homogenate was spun at 1000 x g for 10 minutes at 4 °C in a SS-34 rotor. The supernatant was then spun at 29,000 x g for 20 minutes. The resulting pellet was resuspended in membrane buffer (5 mM Hepes, 0.2% BSA, pH 7.4) to a final concentration of 60 mg original wet weight/ mL.

Gerbil Global Model of Cerebral Ischaemia

Male Mongolian gerbils (Charles River) weighing 60-70 grams are used in these experiments. They are housed in individual cages with food (Purina Rodent Chow) and water available *ad libitum*. The animal room is maintained at 23 ± 2 °C, and is on an automatic 12 hour light cycle.

The gerbils are brought to the surgical suite and dosed intraperitoneally with the test agent or vehicle, forty five minutes prior to surgery. Drugs are administered at a volume of 5 mL/kg (intraperitoneal). Vehicle is generally saline, with sodium phosphate added to adjust pH, if needed. Forty-five minutes after dosing the gerbils are anaesthetised with halothane (3.3%) which is delivered along with oxygen (1.5 l/M) through a face mask. After the gerbils are anaesthetised, halothane is continued at a maintenance level of 1.5-2% along with oxygen. The ventral surface of the neck is shaved and cleaned with alcohol. Surgical procedures are carried out on a thermostat-controlled heating pad set to 37 °C. An incision is made in the neck, the carotid arteries are dissected away from the surrounding tissue, and isolated with a 5 cm length of Silastic tubing. When both arteries have been isolated they are clamped with microaneurysm clips (Roboz Instruments). The arteries are visually inspected to determine that the blood flow has been stopped. After 5 minutes the clips are gently removed from the arteries and blood flow begins again. A sham control group is treated identically but is not subjected to carotid artery occlusion. The incisions are closed with suture and the gerbils removed from the anaesthesia masks and placed on another heating pad to recover from the anaesthesia. When they have regained the righting reflex and are beginning to walk around, they are again dosed with the test compound and returned to their home cages. This occurs approximately five minutes after the end of surgery.

Twenty-four hours post ischaemia gerbils are tested for spontaneous locomotor activity, using a Photobeam Activity System from San Diego Instruments. They are individually placed in Plexiglas chambers measuring 27.5 cm x 27.5 cm x 15 cm deep. The

chambers are surrounded by photocells, and every time a beam is broken one count is recorded. Each gerbil is tested for two hours, and cumulative counts are recorded at 30, 60, 90, and 120 minutes. Mean counts are recorded for each group and drug groups are compared to control with an ANOVA and Bonferroni post test. After each gerbil is tested it is returned to its home cage. At this time gerbils are also observed for any changes from normal behaviour.

For the next two days no specific testing is performed, but the gerbils are observed two to three times per day for any unusual behaviours or obvious neurological symptoms (i.e. ataxia, convulsions, stereotypic behaviour). Four days post ischaemia the gerbils are sacrificed by decapitation and their brains removed and preserved in 10% buffered formalin. Brains were removed, fixed and stained with hematoxylin and eosin. Under a light microscope, hippocampal fields were observed and graded for damage to the CA1 subfield: 0 to 4 scale, with 0 representing no damage and 4 representing extensive damage.

Transient Focal Ischaemia in Rats

The method was as described by Lin, T-N., He, Y.Y., Wu, G., Khan, M. And Hsu, C.Y. Effect of brain edema on infarct volume in a focal model cerebral ischaemia model in rats. Stroke **24**:117-121, 1993, which model is considered to be relevant to the clinical situation. Male Long-Evans rats 250-350 g were used. Surgery leading to focal ischaemia was conducted under anaesthesia with 100 mg/kg ketamine and 5 mg/kg i.m. xylazine. Rectal temperature was monitored and maintained at 37.0 $\pm$ 0.5 °C. The right middle cerebral artery (MCA) was exposed using microsurgical techniques. The MCA trunk was ligated immediately above the rhinal fissure with 10-0 suture. Complete interruption of blood flow was confirmed under an operating microscope. Both common carotid arteries were then occluded using nontraumatic aneurysm clips. After a predetermined duration of ischaemia (45 min), blood flow was restored in all three arteries. Twenty-four hours post occlusion, rats were killed under ketamine anesthesia by intracardiac perfusion with 200 mL of 0.9% NaCl. The brain was removed and processed with 2% triphenyltetrazolium chloride to identify and quantitate the infarcted brain region. Compounds were administered by intravenous infusion for 4 hours.

Data

The following results were obtained in the ^{3}H-Emopamil binding to guinea pig liver membranes test.

Example	IC_{50} (nM)
1	175.5
4	68
7	268

Examples

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated:-

(i) concentrations were carried out by rotary evaporation *in vacuo*;

(ii) operations were carried out at ambient temperature, that is in the range 18-26 °C and under a nitrogen atmosphere otherwise stated;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the formula I were generally confirmed by NMR and mass spectral techniques - proton magnetic resonance spectra were determined in DMSO-δ_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; bs, broad singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, dt, double of triplets, m, multiplet; bm, broad multiplet and unless otherwise stated ^{1}H NMR is quoted; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected, in this application, $(M+H)^+$ is quoted unless otherwise stated;

(vi) intermediates were not generally fully characterised and purity was in general assessed mass spectral (MS) or NMR analysis; and

(vii) in which the following abbreviations (also used hereinabove) may be used :-

DMSO is dimethylsulphoxide;

m/s is mass spectroscopy;

THF is tetrahydrofuran;

DCM	is dichloromethane;
Com Av	is commercially available; and
SM	is starting material.

Example 1

Chroman-4-yl-(2-piperidin-1-ylethyl)amine

4-Chromanone (0.960 g, 6.48 x 10^{-3} mole) and 1-(2-aminoethyl)piperidine (5.163 g, 4.03 x 10^{-2} mole) were combined in toluene (20 mL) and cooled to 0 °C (ice/water/sodium chloride). The mixture was treated with titanium tetrachloride solution (1.0 M in toluene, 3.2 mL, 3.20 x 10^{-3} mole), maintaining the reaction temperature at <5 °C. Upon complete addition, the cooling bath was removed and the mixture stirred at ambient temperature for 24.5 hours. The solid was removed by vacuum filtration and the filtrate concentrated to a yellow oil. A solution of the oil in methanol (15 mL) was treated with sodium borohydride (0.253 g, 6.69 x 10^{-3} mole) and stirred at ambient temperature for 30 minutes. The solvent was evaporated and the residue partitioned between water and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined extracts were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1%NH_4OH:5%MeOH:94%DCM (v/v/v), to give the product as a pale yellow oil (1.15 g, 68%). NMR: 1.27-1.60 (m, 6H), 1.72-1.98 (m, 3H), 2.20-2.45 (m, 6H), 2.57-2.80 (m, 2H), 3.68 (t, 1H), 4.07-4.29 (m, 2H), 6.73 (d, 1H), 6.84 (t, 1H), 7.11 (t, 1H), 7.23 (d, 1H). m/s: 261.

Example 2

Chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine

4-[2-(Piperidin-1-yl)ethylamino]chroman (Example 1) (0.700 g, 2.69 x 10^{-3} mole) was dissolved in methanol (16 mL) and treated with formaldehyde (37% aqueous, 5.4 mL, 7.20 x 10^{-2} mole). After two hours, sodium borohydride (0.975 g, 2.58 x 10^{-2} mole) was added and the mixture was stirred at ambient temperature for 38 hours. The reaction mixture was evaporated and the residue partitioned between water and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined organic portions were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1% NH_4OH:5% MeOH:94% CH_2Cl_2 (v/v/v), to give the product as a colourless oil (0.175 g, 24%). NMR: 1.23-1.57 (m, 6H), 1.80-2.03 (m, 2H), 2.10-2.60 (m, 11H), 3.92-

4.15 (m, 2H), 4.23-4.36 (m, 1H), 6.70 (d, 1H), 6.85 (t, 1H), 7.05 (t, 1H), 7.44 (d, 1H). m/s: 274.

Example 3

(S)-Chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]amine

(a) A suspension of *N*-(*t*-butoxycarbonyl)glycine (2.44 g, 1.39 x 10^{-2} mole) and 1-hydroxybenzotriaole (1.80 g, 1.33 x 10^{-2} mole) in DCM (50 mL) was treated with 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.13 g, 1.63 x 10^{-2} mole) and triethylamine (2.4 mL, 1.72 x 10^{-2} mole), respectively. Immediately, a solution of (*S*)-4-aminochroman (2.00 g, 1.34 x 10^{-2} mole) in DCM (30 mL) was added. After stirring at ambient temperature for 19 hours, the reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to an oil (4.17 g, 100%). ^{1}H NMR (DMSO): 1.39 (s, 9H), 1.80-2.08 (m, 2H), 3.44-3.61 (m, 2H), 4.11-4.26 (m, 2H), 4.94-5.05 (m, 1H), 6.77 (d, 1H), 6.81-7.00 (m, 2H), 7.08-7.20 (m, 2H), 8.24 (d, 1H). m/s: 307.

(b) The oil from step (a) (4.17 g, 1.36 x 10^{-2} mole) in THF (70 mL) was treated with concentrated hydrochloric acid (2 mL) and heated at 60 °C for two hours. Additional concentrated hydrochloric acid (2 mL) was added and heating continued at 60 °C for two hours. The reaction mixture was partitioned between 1N sodium hydroxide solution and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a white solid. The solid was dissolved in DCM and purified by chromatography, eluting with 10% 2.0 M ammonia in methanol:90% DCM (v/v), to give the product as a white solid (2.50 g, 89%). ^{1}H NMR (DMSO): 1.82-2.20 (m, 4H), 3.13 (s, 2H), 4.09-4.27 (m, 2H), 4.95-5.06 (m, 1H), 6.77 (d, 1H), 6.82-6.92 (m, 1H), 7.07-7.22 (m, 2H), 8.17 (d, 1H).

(c) A suspension of the white solid from step (b) (2.50 g, 1.21 x 10^{-2} mole) and sodium carbonate (3.86 g, 3.64 x 10^{-2} mole) in THF (62 mL) was treated with α,α'-dibromo-*o*-xylene (3.19 g, 1.21 x 10^{-2} mole) followed by refluxing for six hours. The reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a white solid. The solid was dissolved in DCM/methanol and purified by chromatography, eluting with 5% 2.0M ammonia in methanol:95% DCM (v/v), to give the product as a white solid (3.51 g, 94%). ^{1}H NMR (DMSO): 1.92-2.08 (m, 2H), 3.42 (s, 2H), 4.00 (s, 4H), 4.16-

4.25 (m, 2H), 5.01-5.13 (m, 1H), 6.76 (d, 1H), 6.83-6.94 (m, 1H), 7.08-7.28 (m, 6H), 8.31 (d, 1H). m/s: 309.

(d) A suspension of the white solid from step (c) (3.51 g, 1.14 x 10^{-2} mole) in THF (115 mL) was treated with lithium aluminum hydride (1.76 g, 4.64 x 10^{-2} mole) and refluxed for two hours. The reaction mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The reaction mixture was filtered through diatomaceous earth and the filtrate evaporated to pink oil which was purified by chromatography, eluting with 5% 2.0M ammonia in methanol:95% DCM (v/v), to give the product as a tan oil (2.49 g, 74%). ^{1}H NMR (DMSO): 1.83-2.30 (m, 3H), 2.67-2.91 (m, 4H), 3.69-3.78 (m, 1H), 3.87 (s, 4H), 4.08-4.32 (m, 2H), 6.73 (d, 1H), 6.77-6.89 (m, 1H), 7.06-7.33 (m, 6H). m/s: 295.

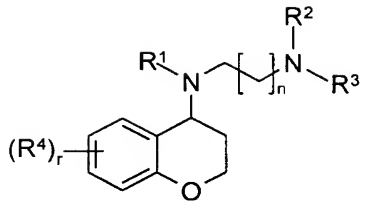
Example 4

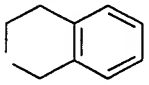
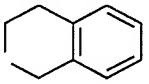
(*S*)-Chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]methylamine

The tan oil from step (d) of Example 3 (1.33 g, 4.52 x 10^{-3} mole) and triethylamine (1.5 mL, 1.08 x 10^{-2} mole) were combined in THF (35 mL) and treated with ethyl chloroformate (0.475 mL, 4.97 x 10^{-3} mole) at ambient temperature. The mixture was stirred for one hour. The reaction mixture was evaporated and the residue was partitioned between water and ethyl acetate. The aqueous portion was extracted with additional ethyl acetate. The combined organic portions were washed (water, brine), dried, and evaporated to a brown oil which was purified by chromatography, eluting with 2:1 ethyl acetate/ hexane (v/v), to give the carbamate as a tan oil (1.49 g, 90%). A solution of the oil in THF (30 mL) was treated with lithium aluminum hydride (0.627 g, 1.65 x 10^{-2} mole) and refluxed for two hours. The reaction mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The reaction mixture was filtered through diatomaceous earth and the filtrate was evaporated to a purple oil which was purified by chromatography, eluting with 5% 2.0 M ammonia in methanol: 95% DCM (v/v), to give te title compound as a tan oil (1.03 g, 82%). ^{1}H NMR (DMSO): 1.84-2.02 (m, 2H), 2.24 (s, 3H), 2.53-2.66 (m, 2H), 2.71-2.92 (m, 2H), 3.83 (s, 4H), 3.95-4.14 (m, 2H), 4.26-4.36 (m, 1H), 6.72 (d, 1H), 6.80-6.90 (m, 1H), 7.03-7.26 (m, 5H), 7.47 (d, 1H). m/s: 309.

Examples 5-10

Using an analogous procedure to that described in Example 3(d), the following compounds were prepared.



Ex	R^1	R^2	R^3	$(R^4)_r$	n	m/s
5	Me	Me	$-CH_2Ph$	H	1	311
6[1]	Me			H	1	323
7[1]	Me	$-CH_2(CH_2)_2CH_2-$		H	1	261
8[1]	H	$-CH_2(CH_2)_4CH_2-$		H	1	275
9[1]	H	Me	$-CH_2Ph$	H	1	297
10[1]	H			H	1	309

[1] S Enantiomer

NMR (DMSO) results:

Example 5: (*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N*,*N'*-dimethylethane-1,2-diamine, 1.80-1.97 (m, 2H), 2.10 (s, 3H), 2.16 (s, 3H), 2.42-2.59 (m, 4H), 3.46 (s, 2H), 3.91-4.11 (m, 2H), 4.23-4.34 (m, 1H), 6.67-6.73 (m, 1H), 6.80-6.87 (m, 1H), 7.02-7.13 (m, 1H), 7.19-7.35 (m, 5H), 7.40-7.45 (m, 1H).

Example 6: (*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]methylamine, 1.82-2.01 (m, 2H), 2.23 (s, 3H), 2.52-2.83 (m, 8H), 3.54 (s, 2H), 3.93-4.12 (m, 2H), 4.25-4.35 (m, 1H), 6.71 (d, 1H), 6.80-6.90 (m, 1H), 6.95-7.14 (m, 5H), 7.46 (d, 1H).

Example 7: (*S*)-chroman-4-ylmethyl-(2-pyrrolidin-1-ylethyl)amine, 1.56-1.68 (m, 4H), 1.80-2.00 (m, 2H), 2.19 (s, 3H), 2.31-2.60 (m, 8H), 3.91-4.11 (m, 2H), 4.23-4.35 (s, 1H), 6.68 (d, 1H), 6.80-6.91 (m, 1H), 7.02-7.15 (m, 1H), 7.44 (d, 1H).

Example 8: (*S*)-(2-azepan-1-ylethyl)chroman-4-ylamine, 1.46-1.63 (m, 8H), 1.83-2.00 (m, 3H), 2.48-2.79 (m, 8H), 3.63-3.72 (m, 1H), 4.07-4.28 (m, 2H), 6.73 (d, 1H), 6.79-6.89 (m, 1H), 7.06-7.16 (m, 1H), 7.22 (d, 1H).

Example 9: (*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N*-methylethane-1,2-diamine, 1.84-1.94 (m, 3H), 2.13 (s, 3H), 2.42-2.55 (m, 2H), 2.63-2.85 (m, 2H), 3.40-3.56 (m, 2H), 3.63-3.72 (m, 1H), 4.07-4.30 (m, 2H), 6.73 (d, 1H), 6.80-6.87 (m, 1H), 7.06-7.17 (m, 1H), 7.19-7.37 (m, 6H).

Example 10: (*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]amine, 1.81-2.12 (m, 3H), 2.53-2.92 (m, 8H), 3.57 (s, 2H), 3.68-3.78 (m, 1H), 4.07-4.29 (m, 2H), 6.72 (d, 1H), 6.77-6.85 (m, 1H), 7.00-7.17 (m, 5H), 7.24 (d, 1H).

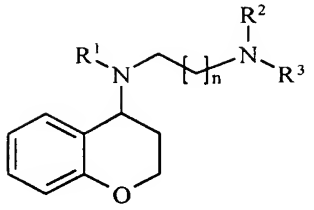
Example 11

N-chroman-4-yl-*N,N',N'*-trimethylpropane-1,3-diamine

4-Chlorochroman (Method A) (0.430 g, 2.30 x 10^{-3} mole) and N,N,N'-trimethyl-1,3-propanediamine (0.710 g, 6.11 x 10^{-3} mole) were combined in acetonitrile (25 mL) and heated at 50 °C for 22 hours. The reaction mixture was evaporated and partitioned between 1M sodium hydroxide and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined organic portion were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1% NH_4OH:10% MeOH:89% DCM (v/v/v), to give the product as a colourless oil (0.314 g, 55%). NMR: 1.47-1.65 (m, 2H), 1.82-1.96 (m, 2H), 2.08 (s, 6H), 2.13 (s, 3H), 2.13-2.49 (m, 4H), 3.94 (t, 1H), 4.00-4.13 (m, 1H), 4.23-4.44 (m, 1H), 6.68 (d, 1H), 6.83 (t, 1H), 7.05 (t, 1H), 7.40 (d, 1H).

Examples 12-20

Using an analogous procedure to that described in Examples 1 or 2, the following compounds were prepared.



Ex	R^1	R^2	R^3	n	By Ex	m/s	SM
12	H	Me	Ph	2	1	319 M+2 3	
13	H	Me	Me	1	1	221	
14	H	$-(CH_2)_2O(CH_2)_2-$		1	1	263	
15	H	$-(CH_2)_2O(CH_2)_2-$		2	1	277	
16	H	H	CH_2Ph	1	1	M+2 3=30 5	
17	H	$-(CH_2)_5-$		2	1	275	
18	H	$-(CH_2)_4-$		2	1	261	
19	H	$-(CH_2)_4-$		1	1	247	
20	Me	Me	Me	1	2	235	Ex 12

NMR results:

Example 12: *N'*-chroman-4-yl-*N*-methyl-*N*-phenylpropane-1,3-diamine, 1.58-1.75 (m, 2H), 1.80-2.00 (m, 3H), 2.45-2.77 (m, 2H), 2.86 (s, 3H), 3.27-3.50 (m, 2H), 3.65 (s, 1H), 4.07-4.30 (m, 2H), 6.57 (t, 1H), 6.64-6.77 (m, 3H), 6.83 (t, 1H), 7.05-7.20 (m, 3H), 7.26-7.33 (m, 1H).

Example 13: *N'*-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine, 1.70-2.00 (m, 3H), 2.14 (s, 6H), 2.33 (t, 2H), 2.55-2.78 (m, 2H), 3.68 (t, 1H), 4.06-4.30 (m, 2H), 6.67-6.90 (m, 2H), 7.04-7.27 (m, 2H).

Example 14: chroman-4-yl-(2-morpholin-4-ylethyl)amine, 1.75-1.95 (m, 3H), 2.27-2.47 (m, 6H), 2.60-2.81 (m, 2H), 3.56 (t, 4H), 3.69 (t, 1H), 4.07-4.30 (m, 2H), 6.73 (d, 1H), 6.84 (t, 1H), 7.11 (t, 1H), 7.25 (d, 1H).

Example 15: chroman-4-yl-(3-morpholin-4-ylpropyl)amine, 1.47-1.68 (m, 2H), 1.82-2.00 (m, 3H), 2.23-2.43 (m, 6H), 2.50-2.76 (m, 2H), 3.54 (t, 4H), 3.66 (t, 1H), 4.06-4.30 (m, 2H), 6.72 (d, 1H), 6.83 (t, 1H), 7.10 (t, 1H), 7.27 (d, 1H).

Example 16: *N*-benzyl-*N'*-chroman-4-ylethane-1,2-diamine, 1.83-1.91 (m, 2H), 1.94-2.20 (m, 2H), 2.52-2.90 (m, 4H), 3.61-3.73 (m, 3H), 4.06-4.30 (m, 2H), 6.72 (d, 1H), 6.83 (t, 1H), 7.10 (t, 1H), 7.17-7.40 (m, 6H).

Example 17: chroman-4-yl-(3-piperidin-1-ylpropyl)amine, 1.23-1.67 (m, 8H), 1.80-2.02 (m, 3H), 2.17-2.40 (m, 6H), 2.50-2.73 (m, 2H), 3.65 (t, 1H), 4.07-4.32 (m, 2H), 6.71 (d, 1H), 7.09 (t, 1H), 7.26 (d, 1H).

Example 18: chroman-4-yl-(3-pyrrolidin-1-ylpropyl)amine, 1.51-2.00 (m, 10H), 2.30-2.80 (m, 7H), 3.62-3.72 (m, 1H), 4.07-4.32 (m, 2H), 6.71 (d, 1H), 6.83 (t, 1H), 7.10 (t, 1H), 7.26 (d, 1H).

Example 19: chroman-4-yl-(2-pyrrolidin-1-ylethyl)amine, 1.60-1.77 (m, 4H), 1.80-2.00 (m, 3H), 2.34-2.57 (m, 6H), 2.60-2.82 (m, 2H), 3.69 (t, 1H), 4.07-4.31 (m, 2H), 6.72 (d, 1H), 6.84 (t, 1H), 7.11 (t, 1H), 7.24 (d, 1H).

Example 20: *N'*-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine, 1.82-2.00 (m, 2H), 2.10 (s, 6H), 2.16 (s, 3H), 2.23-2.56 (m, 4H), 3.90-4.12 (m, 2H), 4.24-4.37 (m, 1H), 6.68 (d, 1H), 6.83 (t, 1H), 7.08 (t, 1H), 7.43 (d, 1H).

Example 21

Chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine bismaleate salt

A solution of chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine (Example 2) (0.170 g, 6.19×10^{-4} mole) in diethyl ether (20 mL) was treated with a solution of maleic acid (0.177 g, 1.52×10^{-3} mole) in diethyl ether (20 mL). The salt form immediately precipitated, adhering to the sides of the flask as a gum. After solidification upon standing overnight, the material was scraped from the sides of the flask, broken up, and collected by vacuum filtration. The solid was vacuum dried at 50 °C for 24 hours to give the salt as a white solid (0.277 g, 88%). NMR: 1.47-1.60 (m, 2H), 1.66-1.84 (m, 4H), 1.91-2.02 (m, 2H), 2.18 (s, 3H), 2.65-2.90 (m, 2H), 3.05-3.34 (m, 6H), 4.00-4.13 (m, 2H), 4.25-4.35 (m, 1H), 6.14 (s, 4H), 6.75 (d, 1H), 6.89 (t, 1H), 7.13 (t, 1H), 7.46 (d, 1H). m/s: 275.

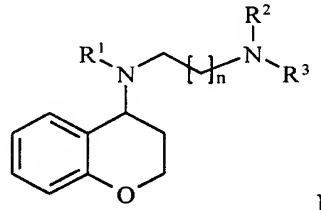
Example 22

4-[3-(*N,N*-Dimethylamino)propyl(*N*-methyl)amino]chroman dihydrochloride

4-[3-(*N,N*-Dimethylamino)propyl(*N*-methyl)amino]chroman (0.314 g, 1.26 x 10^{-3} mole) was dissolved in diethyl ether and treated with an excess of ethereal hydrochloric acid solution. The resulting solid was collected by vacuum filtration under a cloud of nitrogen and vacuum dried at ambient temperature for 20 hours to give the salt as a white solid (0.287 g, 71%). NMR: 2.08-2.48 (m, 4H), 2.62-3.01 (m, 10H), 3.08-3.40 (m, 3H), 4.11-4.20 (m, 1H), 4.32-4.48 (m, 1H), 4.75-4.88 (m, 0.5H), 4.92-5.05 (m, 0.5H), 6.90 (d, 1H), 7.00 (t, 1H), 7.25-7.39 (m, 1H), 7.94-8.08 (m, 1H), 10.51-10.80 (m, 1H), 10.92-11.23 (m, 1H). m/s: 249.

Examples 23-25

Using the procedure of Example 21, salts of the Examples were prepared. The following salts are provided by way of illustration.



Bismaleate

Ex	R^1	R^2	R^3	n	By Ex	m/s
23	H	H	CH_2Ph	1	21	283
24	H	$-(CH_2)_4-$		2	21	261
25	Me	$-(CH_2)_4-$		1	21	261

NMR results:

Example 23: 2.00-2.20 (m, 2H), 3.02-3.24 (m, 5H), 4.09-4.33 (m, 6H), 6.09 (s, 4H), 6.83 (d, 1H), 6.94 (t, 1H), 7.24 (t, 1H), 7.35-7.58 (m, 6H).

Example 24: 1.80-2.30 (m, 8H), 2.89-3.60 (m, 9H, H_2O), 4.27 (t, 2H), 4.42 (s, 1H), 6.04 (s, 4H), 6.89 (d, 1H), 6.99 (t, 1H), 7.31 (t, 1H), 7.42 (d, 1H).

Example 25: 1.85-2.02 (m, 7H), 2.16 (s, 3H), 2.65-2.87 (m, 2H), 3.15-3.43 (m, 5H, H_2O), 4.00-4.13 (m, 2H), 4.25-4.37 (m, 1H), 6.15 (s, 4H), 6.74 (d, 1H), 6.90 (t, 1H), 7.13 (t, 1H), 7.56 (d, 1H).

Example 26

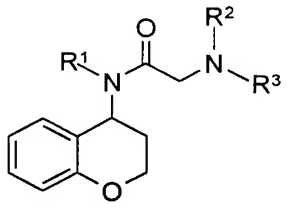
(S)-2-(Benzylmethylamino)-N-chroman-4-ylacetamide

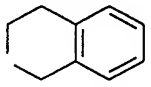
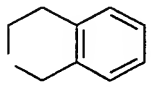
The white solid from Method C (see below) (1.01 g, 4.48 x 10^{-3} mole) and *N*-benzylmethylamine (1.46 g, 1.20 x 10^{-2} mole) were combined in acetonitrile (29 mL) and

refluxed for two hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous portion was extracted with additional ethyl acetate. The combined extracts were washed (water, brine), dried, and evaporated to yield a residue which was purified by chromatography, eluting with 3% 2.0 M ammonia in methanol: 97% DCM (v/v), to give the title compound as an off-white solid (1.25 g, 90%). ^{1}H NMR (DMSO): 1.88-2.08 (m, 2H), 2.20 (s, 3H), 3.05 (s, 2H), 3.59 (s, 2H), 4.13-4.25 (m, 2H), 5.00-5.11 (m, 1H), 6.78 (d, 1H), 6.82-6.91 (m, 1H), 7.07-7.37 (m, 7H), 8.18 (d, 1H). m/s: 311.

Examples 27-31

Using an analogous procedure to that described in Example 26, the following compounds were prepared.



Ex	R^1	R^2	R^3	m/s	SM
27[1]	Me	Me	-CH_2Ph	325	MB
28[1]	Me			337	MB
29[1]	Me	-$CH_2(CH_2)_2CH_2$-		275	MB
30[1]	H	-$CH_2(CH_2)_4CH_2$-		289	MC
31[1]	H			323	MC

[1] S Enantiomer

SM - Starting Material, MB - Method B, MC - Method C

NMR (DMSO) results:

Example 27: (*S*)-2-(benzylmethylamino)-*N*-chroman-4-yl-*N*-methylacetamide, 1.81-2.29 (m, 5H), 2.46 (s, 1.3H), 2.70 (s, 1.7H), 3.23-3.43 (m, 2H), 3.46-3.72 (m, 2H), 4.00-4.38 (m, 2H), 5.35-5.44 (m, 0.4H), 5.76-5.86 (m, 0.6H), 6.74-6.96 (m, 3H), 7.08-7.40 (m, 6H).

Example 28: (*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-methylacetamide, 1.84-2.20 (m, 2H), 2.59-2.97 (m, 6H), 3.26-3.80 (m, 5H), 4.07-4.37 (m, 2H), 5.51-5.61 (m, 0.5H), 5.80-5.89 (m, 0.5H), 6.73-7.20 (m, 8H).

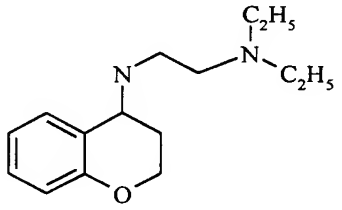
Example 29: (*S*)-*N*-chroman-4-yl-*N*-methyl-2-pyrrolidin-1-ylacetamide, 1.61-1.78 (m, 4H), 1.82-2.20 (m, 2H), 2.40-2.64 (m, 5.2H), 2.70 (s, 1.8H), 3.27-3.48 (m, 2H), 4.08-4.37 (m, 2H), 5.43-5.53 (m, 0.4H), 5.74-5.84 (m, 0.6H), 6.75-6.98 (m, 3H), 7.08-7.19 (m, 1H).

Example 30: (*S*)-2-azepan-1-yl-*N*-chroman-4-ylacetamide, 1.43-1.65 (m, 8H), 1.87-2.11 (m, 2H), 2.57-2.70 (m, 4H), 3.12 (s, 2H), 4.11-4.26 (m, 2H), 4.97-5.09 (m, 1H), 6.77 (d, 1H), 6.80-6.93 (m, 1H), 7.07-7.20 (m, 2H), 8.00 (d, 1H).

Example 31: (*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)acetamide, 1.90-2.09 (m, 2H), 2.70-2.93 (m, 4H), 3.13-3.24 (m, 2H), 3.67 (s, 2H), 4.13-4.25 (m, 2H), 5.02-5.13 (m, 1H),6.75 (d, 1H), 6.82-6.92 (m, 1H), 7.00-7.20 (m, 6H), 8.21 (d, 1H).

Reference Example 1

By the procedure of Example 1 the following compound was prepared:



NMR results: 0.94 (t, 6H), 1.73-2.00 (m, 3H), 2.30-2.80 (m, 8H), 3.68 (t, 1H), 4.05-4.33 (m, 2H), 6.73 (d, 1H), 6.84 (t, 1H), 7.10 (t, 1H), 7.23 (d, 1H); m/s: 249.

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of the starting materials used in the above reactions.

Method A

4-Chlorochroman

4-Chromanol (0.578 g, 3.85 x 10^{-3} mole) was treated with thionyl chloride (2.0 mL, 2.74 x 10^{-2} mole) at ambient temperature. After stirring for 48 hours, the reaction mixture was evaporated. The residue was partially purified by chromatography, eluting with 9:1 hexane:ethyl acetate (v/v) to give the title compound as a tan oil (0.430 g, 66%).

Method B

(*S*)-4-[*N*-Methyl-2-chloroacetamido]thiochroman

(*S*)-*N*-Methyl-4-aminochroman (3.33 g, 2.04 x 10^{-2} mole) and 2,6-lutidine (3.6 mL, 3.09 x 10^{-2} mole) were combined in DCM (45 mL) and cooled to 0 °C (ice/water/sodium chloride). Chloroacetyl chloride (2.0 mL, 2.51 x 10^{-2} mole) was added dropwise, maintaining the reaction temperature at <10 °C. Upon complete addition, the mixture was stirred cold for one hour. The reaction mixture was partitioned between 1N aqueous hydrochloric acid and DCM. The organic portion was washed with additional 1N aqueous hydrochloric acid. The combined aqueous portions were extracted with DCM. The combined organic portions were washed (saturated aqueous sodium bicarbonate, water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1:1 hexane/ethyl acetate (v/v), to give a yellow oil (4.84 g, 99%). ^{1}H NMR (DMSO): 1.85-2.20 (m, 2H), 2.46-2.55 (m, 1H), 2.69 (s, 2H), 4.13-4.39 (m, 2H), 4.43-4.64 (m, 2H), 5.23-5.33 (m, 0.3H), 5.72-5.83 (m, 0.7H), 6.76-7.04 (m, 3H), 7.10-7.22(m, 1H). m/s: 240.

Method C

(*S*)-4-[2-Chloroacetamido]thiochroman

(*S*)-4-Aminochroman (3.42 g, 2.29 x 10^{-2} mole) and 2,6-lutidine (4.0 mL, 3.43 x 10^{-2} mole) were combined in DCM (48 mL) and cooled to 0 °C (ice/water/sodium chloride). Chloroacetyl chloride (2.0 mL, 2.51 x 10^{-2} mole) was added dropwise, maintaining the reaction temperature at <5 °C. Upon complete addition, the mixture was stirred cold for one hour. The reaction mixture was partitioned between 1 N aqueous hydrochloric acid and DCM. The organic portion was washed with additional 1N aqueous hydrochloric acid. The combined aqueous portions were extracted with DCM. The combined organic portions were washed (saturated aqueous sodium bicarbonate, water, brine), dried, and evaporated to a solid. The solid was triturated (hexane), collected, and dried to give a white solid (4.86 g, 94%). ^{1}H NMR (DMSO): 1.82-2.12 (m, 2H), 4.02-4.27 (m, 4H), 4.93-5.04 (m, 1H), 6.79 (d, 1H), 6.84-6.95 (m, 1H), 7.09-7.23 (m, 2H), 8.74 (d, 1H).

Example 32

Following conventional procedures well known in the pharmaceutical art the following representative pharmaceutical dosage forms containing a compound of formula (I) can be prepared:

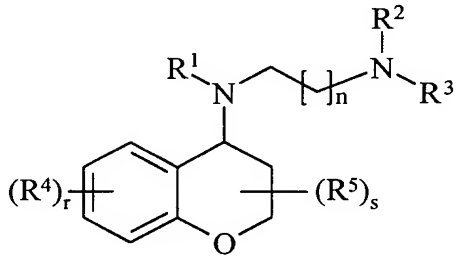
(a)	Tablet	mg/tablet
	Compound of Formula I	50.0
	Mannitol, USP	223.75
	Croscarmellose sodium	60
	Maize starch	15.0
	Hydroxypropylmethylcellulose (HPMC), USP	2.25
	Magnesium stearate	3.0
(b)	Capsule	mg/capsule
	Compound of Formula I	10.0
	Mannitol, USP	488.5
	Croscarmellose sodium	15.0
	Magnesium stearate	1.5

(c) Injection

For intravenous administration, a compound of Formula I is dissolved in an isotonic sterile solution (5 mg/mL).

CLAIMS:

1. A method of treating neurological disorders comprising administration of a therapeutically-effective amount of any compound according to formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally

substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl;

R^4 at each occurrence is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R^4 may be the same or different; and

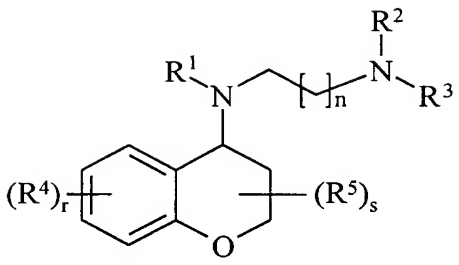
s is 0, 1, 2 or 3 wherein at each occurrence the value of R^5 may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

2. The method according to Claim 1, for treating stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia.

3. The method according to Claim 1, for treating neurological disorders treatable by inhibition of the the [^{3}H]-emopamil binding site.

4. A pharmaceutical composition comprising any compound according to formula (I), or a *in vivo*-hydrolysable ester, amide or carbamate thereof, together with a pharmaceutically-acceptable carrier, wherein, in a compound of formula (I):



(I)

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}

$_6$alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl;

R^4 at each occurrence is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R^4 may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the value of R^5 may be the same or different;

or a pharmaceutically-acceptable salt thereof.

5. A pharmaceutical composition according to Claim 4, comprising any compound in accord with formula (I), wherein:

R^1 is hydrogen or C_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic ring;

r is 0;

s is 0;

n is 1 or 2.

6. A pharmaceutical composition according to Claim 6, comprising any compound in accord with formula (I), wherein:

R^1 is hydrogen or methyl;

R^2 and R^3 are independently selected from methyl, ethyl or benzyl,

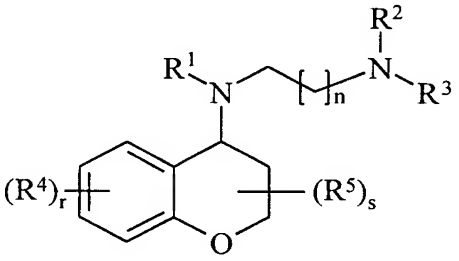
or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a ring selected from pyrrolidin-1-yl, piperidin-1-yl and morpholino.

7. A pharmaceutical composition according to Claim 6, comprising any compound in accord with formula (I), wherein:

R^2 and R^3 are independently selected from methyl or benzyl,

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a ring selected from pyrrolidin-1-yl and piperidin-1-yl.

8. Any compound according to formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a

heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl;

R^4 at each occurrence is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R^4 may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the value of R^5 may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof;

with a proviso wherein in such compounds:

if r is 1, R^4 is a 6-linked cyano moiety, s is 2 and both R^5 moieties are 2-linked methyl, n is 1, and R^1 and R^2 are both H, then R^3 is not phenyl or benzyl;

if r and s are both 0, R^1 is H and n is 2, then R^1 and R^2 are not both ethyl or not both H, or

if r and s are both 0, R^1 is H and n is 1, then R^1 and R^2 are not both ethyl.

9. A compound according to Claim 8, wherein:

R^1 is hydrogen or C_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic ring;

r is 0;

s is 0;

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

10. A compound according to Claim 9, wherein:

R^1 is hydrogen or methyl;

R^2 and R^3 are independently selected from methyl, ethyl or benzyl,

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a ring selected from pyrrolidin-1-yl, piperidin-1-yl and morpholino;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

11 A compound according to Claim 10, wherein:

R^2 and R^3 are independently selected from methyl or benzyl,

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a ring selected from pyrrolidin-1-yl and piperidin-1-yl;

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

12. A compound according to Claim 8, selected from:

chroman-4-yl-(2-piperidin-1-ylethyl)amine;

chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine;

(*S*)-chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]amine;

(*S*)-chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]methylamine

(*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N*,*N'*-dimethylethane-1,2-diamine;

(*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]methylamine;

(*S*)-chroman-4-ylmethyl-(2-pyrrolidin-1-ylethyl)amine;

(*S*)-(2-azepan-1-ylethyl)chroman-4-ylamine;

(*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N*-methylethane-1,2-diamine;

(*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]amine;

N-chroman-4-yl-*N,N',N'*-trimethylpropane-1,3-diamine;

N'-chroman-4-yl-*N*-methyl-*N*-phenylpropane-1,3-diamine;

N'-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine;

chroman-4-yl-(2-morpholin-4-ylethyl)amine;

chroman-4-yl-(3-morpholin-4-ylpropyl)amine;

N-benzyl-*N'*-chroman-4-ylethane-1,2-diamine;

chroman-4-yl-(3-piperidin-1-ylpropyl)amine;

chroman-4-yl-(3-pyrrolidin-1-ylpropyl)amine;

chroman-4-yl-(2-pyrrolidin-1-ylethyl)amine;

N'-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine;

(*S*)-2-(benzylmethylamino)-*N*-chroman-4-ylacetamide;

(*S*)-2-(benzylmethylamino)-*N*-chroman-4-yl-*N*-methylacetamide;

(*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-methylacetamide;

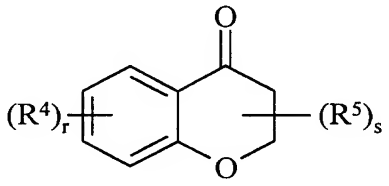
(*S*)-*N*-chroman-4-yl-*N*-methyl-2-pyrrolidin-1-ylacetamide;

(*S*)-2-azepan-1-yl-*N*-chroman-4-ylacetamide, and

(*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)acetamide.

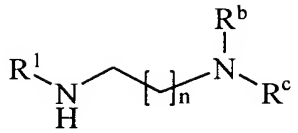
13. A method of making a compound of formula (I) according to Claim 8, wherein R^1, R^2, R^3, R^4, R^5, s, r and n unless otherwise defined are as defined in Claim 8, said method comprising:

a) reacting a ketone of formula (II):



(II)

with an amine of formula (III):

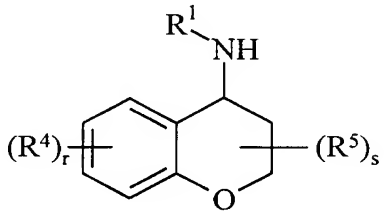


(III);

wherein R^b and R^c are R^2 and R^3 respectively, unless the value of R^2 and/or R^3 is hydrogen, in which case the appropriate R^b and/or R^c is a suitable amino protecting group such as those defined below;

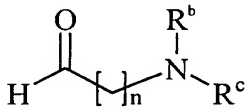
or

b) reacting an amine of formula (IV):



(IV)

with an aldehyde of formula (V):

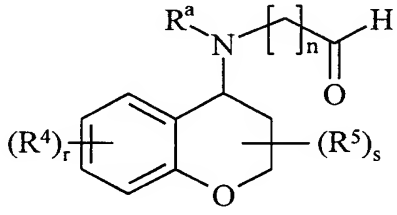


(V)

wherein R^b and R^c are as defined above;

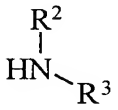
or

c) reacting an aldehyde of formula (VI):



(VI)

with an amine of formula:

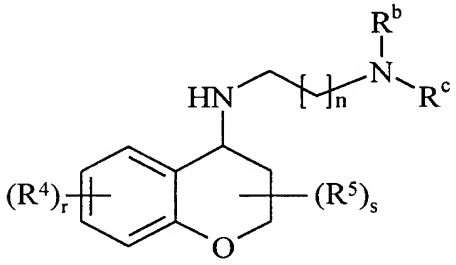


(VII)

wherein R^a is R^1 unless the value of R^1 is hydrogen, in which case R^a is a suitable amino protecting group such as those defined below;

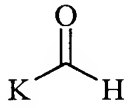
or

d) if R^1 is C_{1-6}alkyl, reacting a compound of formula (VIII):



(VIII)

wherein R^b and R^c are as defined above, with a compound of formula (IX);

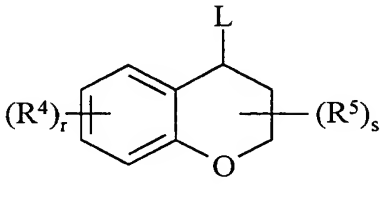


(IX)

wherein K is hydrogen or C_{1-5}alkyl;

or

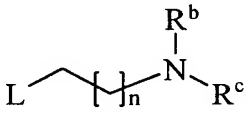
e) reacting a compound of formula (X):



(X)

wherein L is a suitable displaceable group, with an amine of formula (III); or

f) reacting an amine of formula (IV) with a compound of formula (XI):

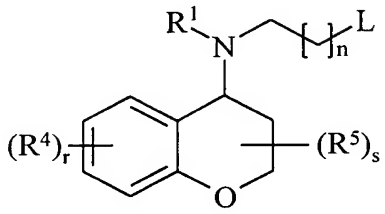


(XI)

wherein L is a suitable displaceable group and R^b and R^c are as defined above;

or

g) reacting a compound of formula (XII):



(XII)

wherein L is a suitable displaceable group, with an amine of formula (VII);

or

h) if R^1 is not hydrogen, reacting a compound of formula (VIII) with a compound of formula (XIII):

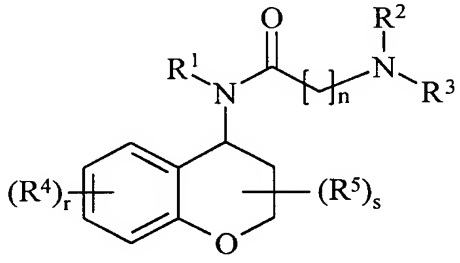
R^1-L

(XIII)

wherein L is a suitable displaceable group;

or

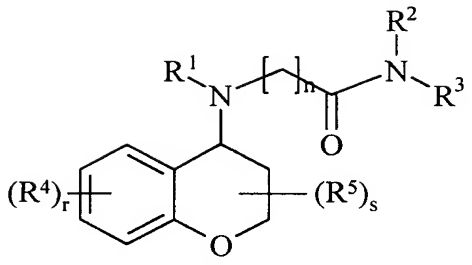
i) reducing a compound of formula (XIV):



(XIV)

or

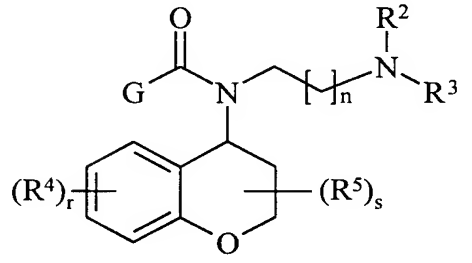
j) reducing a compound of formula (XV):



(XV)

or

k) if R^1 is not hydrogen, reducing a compound of formula (XVI):



(XVI)

where:

for preparing a compound wherein R^1 is methyl, G is a suitable displaceable group;

or

for preparing a compound wherein R^1 is C_{2-6}alkyl, G is C_{1-5}alkyl;

and thereafter if necessary:

converting a compound of the formula (I) into another compound of the formula (I);

removing any protecting groups; or

forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 00/02304

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/68 C07D405/12 A61K31/353 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	FR 2 670 780 A (SYNTHELABO S.A.) 26 June 1992 (1992-06-26) pages 8-11, table; page 13, formula II --- -/--	9-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2000	01/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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X	EVANS J.M.: "Synthesis and antihypertensive activity of substituted trans-4-amino-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ols" JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, no. 11, November 1983 (1983-11), pages 1582-1589, XP002152682 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 table I, compound 12 ---	9-11
X	DING C.Z.: "Synthesis of 4-(N-alkyl-N-heteroaryl)amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile derivatives via an unusual 1,4-oxygen to nitrogen heteroaryl migration" TETRAHEDRON LETTERS., vol. 37, no. 26, 24 June 1996 (1996-06-24), pages 4447-4450, XP002152683 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 table 1, entry 5, starting material ---	9-11
X	EP 0 359 537 A (BEECHAM GROUP PLC) 21 March 1990 (1990-03-21) page 9, compound D3 ---	9-11
X	EP 0 587 180 A (E.R. SQUIBB & SONS, INC.) 16 March 1994 (1994-03-16) page 31, example 33A ---	9-11
Y	WO 98 00412 A (SCHERING CORP.) 8 January 1998 (1998-01-08) the whole document ---	1,2,4-7
Y	WO 97 31887 A (ZENECA LTD.) 4 September 1997 (1997-09-04) the whole document ---	1,2,4-7
Y	FR 2 687 401 A (LES LABORATOIRES MERAM) 20 August 1993 (1993-08-20) the whole document ---	1,2,4-7
P,Y	WO 99 32461 A (ZENECA LTD.) 1 July 1999 (1999-07-01) the whole document ---	1-13
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INTERNATIONAL SEARCH REPORT

Intern. ..al Application No
PCT/GB 00/02304

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

Internal Application No
PCT/GB 00/02304

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